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direct or inverted repeat sequences. Although such deletions could be attributed to instability of the CFTR cDNA in *E. coli*, computer analysis of the CFTR sequence did not reveal an unusual number of direct and inverted sequence repeats within the published CFTR sequence, thereby indicating that the CFTR cDNA should not be inherently unstable in *E. coli*.-

STATEMENTS

In advance of the telephonic interview of this case scheduled for Wednesday, November 23, 1994 at 10:00 a.m., Applicants respectfully request that the following further remarks also be made of record. The remarks are provided as additional helpful background for the interview and to further highlight:

- (1) the scientific importance of Applicants' discoveries as claimed herein;
- (2) the time frame of those discoveries in relation to the prior art; and
- (3) to address any issues under Section 112 that may remain from the Examiner's Action of June 16, 1994.

Remarks:

As commented in Applicants' paper mailed December 22, 1992 at pages 5-6 thereof, and Applicants' paper mailed October 3, 1994 at pages 6-7 thereof, substantial and unexpected difficulties prevented the production of stable, recoverable, full length CFTR-encoding DNA suitable for cloning. Applicants' patent application is the first to disclose unobvious solutions to these unexpected difficulties. It is again respectfully submitted that neither any patent application including any application to which U.S. Patent No. 5,240,846 claims priority that was filed before September 18, 1990 (the filing date of the 07/584,275 application, the latest of the parent applications for the '846 patent), nor any publication available before said date, discloses either the existence of, or the solution to, the severe difficulties that prevented production of DNA encoding the recombinant cystic fibrosis transmembrane conductance regulator (CFTR) polypeptide - a problem first recognized and solved by Applicants.

In this regard, Applicants would respectfully direct attention to the enclosed copy of Drumm et al., "The Full Length CFTR cDNA is Toxic in